versus soft-seed feeders consisted of univariate *t*-tests on all seven morphological variables; in all cases birds feeding on large seeds were significantly larger ($P < .0001$) than those feeding only on small seeds. The seven-variable multivariate analysis of variance between the two groups was also highly significant [$F(7,311) = 7.94$, $P < .0001$]. The standardized coefficients of the discriminant function separating the two feeding groups weighted bill depth most heavily (.80), followed by wing chord (.57), with all other variables having coefficients under .25. This underlines the link between bill depth and feeding behavior, which persisted among the survivors at the end of 1977 (P. R. Grant, *Anim. Behav.* in press).

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11. Separate linear discriminant functions were computed for males alone, for females alone, and for both combined with mature birds of uncertain sex, each maximizing the distance between the centroids of survivors and nonsurvivors in that group. Unstandardized discriminant scores were calculated for each bird by using the appropriate equation. The variances for the seven original variables, the first and second principal components, and the discriminant function of birds that survived from June 1976 to March 1978 were compared with those of birds that disappeared. The ten comparisons were made for males, for females, and for the combined group; in 21 of the 30 comparisons the selected group was less variable, but none of the 30 *F*-tests approached significance.
12. We computed *t*-tests for the 30 comparisons detailed in (*11*), again contrasting survivors and nonsurvivors to maintain sample independence. After the 1977 drought, males were significantly larger ($P < .01$) in all variables except wing chord, tarsus length, and principal component 2. Females were significantly larger ($P < .05$) in all variables except weight and tarsus length, with principal component 2 on the borderline ($P = .066$). The combined group was significantly larger ($P < .001$) in all variables except principal component 2.
13. The three largest standardized coefficients of the discriminant function for males alone were for bill depth (1.00), weight (.85), and bill width (.56), and the three largest $\Delta\bar{w}/\bar{w}$ values for male univariate characters were again for bill depth (.22), weight (.20), and bill width (.15). The corresponding results for the female group were different; the largest standardized discriminant function coefficients were for bill length (− 1.21), bill length at a depth of 4 mm (.90), and bill depth (.55), and the largest $\Delta\bar{w}/\bar{w}$ values were for bill length at a depth of 4 mm (.40), bill depth (.25), wing cord (.22), bill length (.20), and bill width (.20).
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Heart Imaging with Cationic Complexes of Technetium

Abstract. *The cationic technetium-99 complex* trans-$[^{99}Tc(dmpe)_2Cl_2]^+$, *where dmpe is bis(1,2-dimethylphosphino)ethane or* $(CH_3)_2P–CH_2CH_2–P(CH_3)_2$, *has been prepared and characterized by single-crystal, x-ray structural analysis. The technetium-99*m *analog,* trans-$[^{99m}Tc(dmpe)_2Cl_2]^+$, *has also been prepared and shown to yield excellent gamma-ray images of the heart. The purposeful design, characterization, and synthesis of this technetium-99*m *radiopharmaceutical represents a striking application of fundamental inorganic chemistry to a problem in applied nuclear medicine.*

In the practice of diagnostic nuclear medicine, some chemical form of a photon-emitting isotope is administered to a patient with the goal of having this isotope localize in a specific organ. Subsequent scanning of the organ with a gamma-ray camera provides valuable diagnostic and prognostic information by an essentially noninvasive technique (*1, 2*). Technetium-99*m* is the isotope of choice for diagnostic nuclear medicine because of its optimal nuclear properties, its diverse chemistry, and its general availability (*3*). With the use of ^{99m}Tc in various chemical forms, it is now possible to image a variety of organs, including the brain, kidneys, lungs, liver, and bones; fully 85 percent of all diagnostic procedures in nuclear medicine are performed with ^{99m}Tc (*4*). However, it has not yet been possible to image normal heart muscle with a ^{99m}Tc radiopharmaceutical. It is estimated that in 1977 over 600,000 deaths in this country were attributable to myocardial infarction (heart attack) (*5*), and it has been noted (*5*) that many of these deaths could be eliminated if the high-risk patient could be identified at the earliest possible time. It has thus been a long-standing, but elusive, goal of diagnostic nuclear medicine to develop a ^{99m}Tc radiopharmaceutical that would accumulate in normal heart tissue and thereby allow the early evaluation of the extent of damage resulting from myocardial infarction (*6*).

It is known that isotopes of the group I cations accumulate in normal heart tissue, ^{43}K, ^{81}Rb, and ^{129}Cs all having been used to provide gamma-ray images of the heart (*7*). It is also generally accepted that these cations accumulate through involvement with the Na^+, K^+-dependent adenosinetriphosphatase system; that is, they function as K^+ analogs. On this basis it was suggested that Tl(I) might also function as a K^+ analog and therefore accumulate in the heart (*8*). Thallium(I) does indeed localize in heart tissue, and ^{201}Tl is currently the agent of choice for myocardial imaging (*9*). However, relative to ^{99m}Tc, ^{201}Tl is a poor radionuclide for procedures in nuclear medicine; it is expensive, it has a photon energy that is too low for optimum imaging, and a large dose must be administered to the patient in order to obtain a reasonably high count rate (*10*). We postulated that +1-charged complexes of ^{99m}Tc might mimic the in vivo behavior of Tl(I) and be taken up by normal heart tissue (*11*). Prior to this work (*11*), no cationic complexes of ^{99m}Tc had been prepared and evaluated as radiopharmaceuticals as far as we know, presumably because knowledge was lacking about the synthetic and coordination chemistry of technetium. We report here on the preparation, characterization, and evaluation as a potential heart-imaging agent of a water-soluble, +1-charged complex of technetium.

Using milligram amounts of ^{99}Tc, one can prepare cationic complexes of Tc(III) by the reaction of chelating phosphine or arsine ligands (D) with the readily available hexahalogenotechnetium(IV) complexes TcX_6^{2-} (X = Cl, Br, I) (*11, 12*):

$$TcX_6^{2-} + \text{excess D} \xrightarrow{\text{ethanol/H}_2\text{O/HX}} TcD_2X_2^+$$

This reaction depends upon the reducing power of the excess arsine or phosphine ligand to convert Tc(IV) to Tc(III). When D is dmpe, or bis(1,2-dimethlyphosphino)ethane, $(CH_3)_2P–CH_2CH_2–P(CH_3)_2$, the cationic product is water-soluble and is readily purified by aqueous ion-exchange chromatography. The $[Tc(dmpe)_2X_2]^+$ complexes may also be prepared from pertechnetate, TcO_4^-, the chemical form in which technetium is provided by the commercial ^{99m}Tc generators used in hospitals (*1*). In this case also, the reducing power of the excess phosphine ligand converts Tc(VII) to Tc(III):

$$TcO_4^- + \text{excess dmpe} \xrightarrow{\text{ethanol/H}_2\text{O/HX}} Tc(dmpe)_2X_2^+$$

This preparation is readily conducted in greater than 90 percent yield using "no carrier added" $^{99m}TcO_4^-$ produced from commercial generators.

The $[Tc(dmpe)_2X_2]^+$ complexes are readily identified in terms of their

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characteristic visible-ultraviolet spectra, which are dependent on the nature of X (*13*). When recrystallized from 95 percent ethanol, the trifluoromethanesulfonate salt of the chloro complex, $[Tc(dmpe)_2Cl_2]F_3CSO_3$, forms single crystals suitable for x-ray diffraction analysis. These crystals belong to the monoclinic class [space group $P2_1/c$; Z (number of formula units per unit cell) = 4; a = 8.076(2) Å, b = 24.401(4) Å, c = 13.435(4) Å (the number in parentheses is the standard deviation of the last significant digit), β (crystallographic angle between a and c) = 96.61(2)°; calculated density = 1.56 g/cm^3; observed density = 1.65 g/cm^3]. The structure was solved by standard Patterson and Fourier methods based on the use of 3331 independent reflections [$I > 2\sigma(I)$ (I is intensity and σ is the standard deviation), $2\theta < 47.6°$ (θ is the diffraction angle), Mo Kα radiation]. Final least-squares refinement of 244 parameters converged with a conventional discrepancy index (R_1) (*14*) of 0.056. The structure of the $[Tc(dmpe)_2Cl_2]^+$ cation is shown in Fig. 1, the *trans* octahedral coordination geometry being typical for Tc(III) $[TcD_2X_2]^+$ cations (D = chelating ditertiary arsine or phosphine, X = halogen) (*15*). The large values of the thermal parameters associated with the carbon atoms of the dmpe ligand, and discrepancies between chemically equivalent ligand bond lengths, indicate that there is some conformational disorder of these ligands.

Figure 2 shows images obtained at various times after a saline solution of $[^{99m}Tc(dmpe)_2Cl_2]^+$ has been intravenously injected into a dog. To obtain these images, the anesthetized dog is placed on its back and the gamma-ray camera is positioned over the chest area. Immediately after injection the $[^{99m}Tc(dmpe)_2Cl_2]^+$ radiopharmaceutical is in the blood pool, which in this anatomical region is predominantly within the heart chambers. Thus, in the image labeled "0 minutes" the blood pool appears as a "hot" or "positive" image, and the heart muscle appears as a "cold" or "negative" image surrounding the blood pool. At later times the activity disappears from the blood and appears in the heart muscle, as well as in the liver and gallbladder. Now the heart muscle appears as a "positive" image surrounding the "cold" blood pool—this is the characteristic doughnut-shaped pattern obtained with other heart-imaging agents such as ^{201}Tl. As with ^{201}Tl, the heart image is generated by only a few percent of the injected dose; the bulk of the radiopharmaceutical is taken up by the liver and kidneys in the course of the normal functioning of these organs. In humans, the kidneys, liver, and gallbladder are sufficiently displaced from the heart that accumulation of activity by these organs does not interfere with the obtaining of useful heart images. Thus far, there are no indications that the $[^{99m}Tc(dmpe)_2Cl_2]^+$ agent is in any way toxic, but extensive toxicity studies are yet to be performed.

The successful imaging of the heart by $[^{99m}Tc(dmpe)_2Cl_2]^+$ represents one of the very few times in the annals of nuclear medicine where the exact structure of the ^{99m}Tc radiopharmaceutical (Fig. 1) generating the gamma-ray images (Fig. 2) is known with certainty. It also represents one of the very few examples of the purposeful design, characterization, and synthesis of a ^{99m}Tc radiopharmaceutical. The groundwork is now laid for a systematic variation in the ligands of $[^{99m}TcD_2X_2]^+$ complexes in order to develop structure-activity relationships and eventually the complex that most efficaciously images the heart. The success of this endeavor will depend upon continued synergistic interactions among disciplines and agencies.

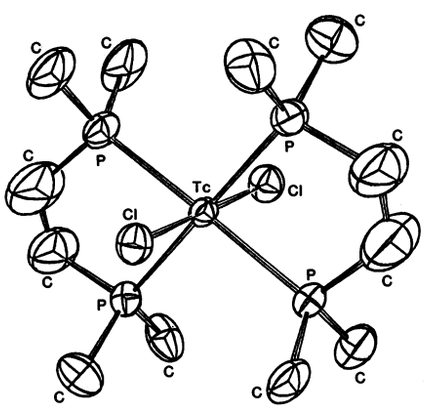

Fig. 1. Structure of $[^{99}Tc(dmpe)_2Cl_2]^+$. The ellipsoids represent 50 percent probability. The cation has no crystallographically imposed symmetry but is of approximate symmetry D_{2h}. Average bond lengths are as follows: Tc–Cl, 2.323(3) Å; Tc–P, 2.436(5) Å. Bond angles are as follows: Cl–Tc–Cl, 179.5(13)°; average Cl–Tc–P, 89.3(4)°; average intraligand P–Tc–P, 81.4(2)°.

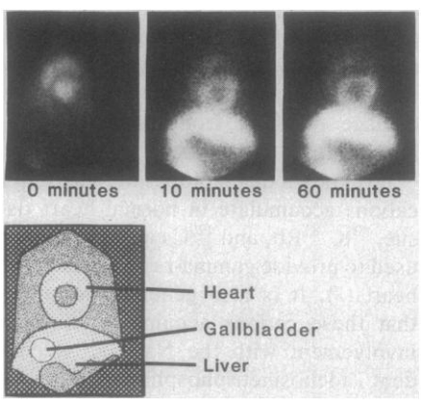

Fig. 2. Gamma-ray images of the chest of a dog (anterior view) after injection of $[^{99m}Tc(dmpe)_2Cl_2]^+$. Immediately after injection the activity is in the blood pool, primarily within the heart, and the heart muscle appears as a "negative" image. At later times the activity is taken up by the heart muscle, leading to "positive" visualization of the heart in the characteristic doughnut-shaped image.

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